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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/749,025	12/27/2000	Petrus Johannes Maria Nuijten	99511 US	6121

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	17

DATE MAILED: 01/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/749,025	NUIJTEN ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-11,14,17 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8,10,11,14,17 and 18* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 7, 2002 has been entered.

2. Applicant's amendment is acknowledged. Claims 6-7, 14 and 17-18 have been amended. Claims 1-5 and 15-16 have been cancelled. Applicant's declaration is filed December 12, 2002 is acknowledged.

3. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

4. In view of Applicant's amendment the following objections and rejections are withdrawn:

a) Objection of claim 14, page 5, of the previous Office action.
b) Rejection of claim 6 under 35 U.S.C. 112, first paragraph, pages 2-4, paragraph 4 of the previous Office action.
c) Rejection of claims 14, 16 and 18 under 35 U.S.C. 102(b), page 8, paragraph 9 of the previous Office action.

Rejections Maintained

5. The rejection under 35 U.S.C. 102(a) as anticipated by Allen-Vercoe et al is maintained for claim 6 for the reasons set forth on pages 5-6, paragraph 7 of the previous Office Action.

The rejection was on the grounds that Allen-Vercoe et al teach a *Salmonella enteritidis* mutated bacterium that in its wild type form carries flagella and said mutated bacterium lacking at least one antigenic determinant of flagellin or flagella found in its wild form. Allen-Vercoe et al teach that isolated bacteria colonies were diluted using phosphate buffered saline and the inocula were administered immediately (page 396, 2nd column). Limitations such as the vaccine in a freeze-dried or spray-dried form are being viewed as process limitations.

Since the Office does not have the facilities for examining and comparing applicant's mutated bacterium with the mutated bacterium of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the mutated bacterium of the prior art does not possess the same material structural and functional characteristics of the claimed mutated bacterium). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that claim 6 has been amended so that it includes the elements of a "mutated bacterium lacking at least one antigenic determinant of flagellin or flagella found in its wild type form and having the same immunological characteristics as the bacterium strain deposited as CBS 108995". Applicant urges that Allen-Vercoe et al do not discuss antigenic determinants and therefore do not anticipate the claimed invention. Applicant urges that Allen-Vercoe et al do not teach a vaccine and does not demonstrate induction of a protective response.

Applicant's arguments filed October 7, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the record to show that the mutated bacterium of the prior art is not the same as the claimed mutated

bacterium. Claim 6 is directed to a mutated bacterium that in its wild type form carries flagella, said mutated bacterium lacking at least one antigenic determinant of flagellin or flagella found in its wild type form and having the same immunological characteristics as the bacterium strain deposited CBS 108995". It should be noted that claim 6 does not recite a "vaccine". Allen-Vercoe et al teach mutants of *Salmonella enterica* serotype *Enteritidis* that are unable to express flagella but retain the genetic potential to express fimbriae, a flagellate but multiply afimbriate mutant (defective for the elaboration of five different fimbrial types) and a flagellate but non-motile "paralyzed" mutant. The *Salmonella enterica* serotype *Enteritidis* mutants of Allen-Vercoe et al, lack at least one antigenic determinant of flagella found in its wild type form since they are unable to express flagella but retain the genetic potential to express fimbriae. The mutants of Allen-Vercoe et al appear to have the same immunological characteristics as the deposited mutated bacterium CBS 108995. Therefore, the mutants of Allen-Vercoe et al anticipate the claimed invention.

6. The rejection under 35 U.S.C. 102(b) as anticipated by Marjarian et al is maintained for claims 6-8 and 10-11 for the reasons set forth on pages 6-7, paragraph 8 of the previous Office Action.

The rejection was on the grounds that Marjarian et al teach the use of a live attenuated *Salmonella dubin* strain (SL5927) that is non-flagellated (and thus non-motile) and lacks at least one antigenic determinant of flagellin or flagella found in its wild form (pages 59 and 66-67). Marjarian et al teach that strain SL5927 comprises a plasmid containing a foreign epitope (i.e. SL5928)(pages 68). Marjarian et al teach that rabbits were immunized with SL5928 (i.e. non-flagellated and thus non-motile) comprising a plasmid containing a foreign epitope (pages, 79-80). Marjarian et al teach that oral administration of the live attenuated *S. dublin* SL9528 expressing the hybrid flagella were carried out in rabbits, mice and guinea pigs (page 81). Marjarian et al

teach that vaccine used in the invention are formulated with adjuvants (page 4). Limitations such as the vaccine in a freeze-dried or spray-dried form is being viewed as process limitations.

Since the Office does not have the facilities for examining and comparing applicant's mutated bacterium with the mutated bacterium of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the mutated bacterium of the prior art does not possess the same material structural and functional characteristics of the claimed mutated bacterium). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Marjarian et al is directed to bacteria carrying recombinant flagella carrying heterologous epitopes. Applicant also urges that Marjarian et al disclose vaccines that either consist of subunit flagellar proteins or live attenuated bacteria expressing flagella from recombinant plasmids. Applicant urges that the Office Action states that "Marjarian et al teach the use of a live attenuated *Salmonella dubin* (SL5927) that is non-flagellated (and thus non-motile) and lacks at least one antigenic determinant of flagellin or flagella found in its wild form (pages 59 and 66-67)". Applicant urges that Marjarian et al approach requires that the flagellin gene be present. Applicant urges that Marjarian et al states that "the recombinant flagellin proteins are exported to the cell surface wherein they assemble into functional flagella containing the heterologous epitope". Applicant urges that Marjarian et al does not disclose flagellin minus bacteria as vaccines *per se* and the bacteria of Marjarian et al are employed as live vectors that enable expression of the recombinant flagellum within the infected host cell, through expression from an inserted plasmid carrying a flagellin gene-construct. Applicant urges that amended claims 6 and 7, with claims 8-11 dependent therefrom, define over this reference.

Applicant's arguments filed October 7, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that Applicant appears to argue limitations that are not in the claims. Claims 6-8 and 10-11 are drawn to a mutated bacterium that in its wild type form carries flagella, said mutated bacterium lacking at least one antigenic determinant of flagellin or flagella found in its wild type form and having the same immunological characteristics as the bacterium strain deposited CBS 108995 and a vaccine for the protection of animals against Salmonellosis comprising an immunologically effective of the mutated bacterium or antigenic material thereof. There is no requirement in the claims that the flagellin gene in the mutated bacterium be absent. Marjarian et al disclose a mutated bacterium with the disclosure of attenuated *Salmonella dublin* strain (SL5927)) which is nonflagellated (thus nonmotile) (i.e. lacking at least one antigenic determinant of flagellin or flagella found in its wild type form) used in vaccines (pages 59 and 66-67). There is no requirement that the claimed vaccines should be minus bacteria. Marjarian et al disclose several different type of vaccines in the invention. Marjarian et al disclose recombinant flagellin fusion genes and proteins that can be formulated for use in subunit vaccines (page 12), disclose live vaccines that are live attenuated bacteria that comprise heterologous epitopes (page 43) and Marjarian et al disclose heterologous peptides that express a recombinant flagellin fusion protein that may be used as an immunogen in subunit vaccines, which may be multivalent (page 45). It should be noted that the subunit vaccines of Marjarian et al comprising recombinant flagellin fusion proteins do not require that the gene is present and do not require host bacteria. Applicant asserts that "the bacteria of Marjarian et al

are employed as live vectors that enable expression of the recombinant flagellum within the infected host cell, through expression from an inserted plasmid carrying a flagellin gene-construct", this is only one embodiment of the claimed invention. It is the Examiner's position that there is nothing on the record to show that the mutated bacterium and vaccines of the prior art is not the same as the claimed mutated bacterium and vaccines. Therefore, the mutated bacterium and live attenuated vaccines of Marjarian et al anticipate the claimed mutated bacterium and vaccine.

7. The rejection under 35 U.S.C. 102(b) as anticipated by Marjarian et al is maintained for claims 14 and 17-18 for the reasons set forth on pages 9-10, paragraph 10 of the previous Office Action.

The rejection was on the grounds that Marjarian et al teach recombinant flagellin vaccine formulations (see the Title). Marjarian et al teach attenuated invasive bacteria expressing the recombinant flagellin genes of the invention used in live vaccine formulations (see the Abstract). Marjarian et al teach that the coding region from the H1-d flagellin gene is present in a 3.8 kb EcoRI genomic fragment and contains two restriction sites and that an additional *Eco*RV site is present. Marjarian et al teach that two subclones were constructed by the insertion of the 3.8 kb genomic fragment into the *Eco*RI site. Marjarian et al teach that a 51 bp *Eco*RV fragment was deleted from each of the subclones which resulted in a unique *Eco*RV restriction site available for insertion of oligonucleotides specifying a foreign epitope (page 14 and Figure 1). Marjarian et al teach that recombinant flagellin proteins are exported to the cell surface where they assemble into functional flagella containing the heterologous (foreign) epitope. Marjarian teach that recombinant flagellin fusion proteins provoke a cellular, mucosal or humoral response (page 11). Marjarian et al teach that *Salmonella* species which in attenuated forms can be used in the vaccine formulations of this invention are *S. typhi, S, typhimurium, S. paratyphi A, S. paratyphi B and S. enteritidis serotype dublin* (Table II, page 40 and claim 41, page 104). Marjarian et al further teach that the vaccine formulations of their invention are often formulated and inoculated with various adjuvants. Marjarian et al teach examples of suitable adjuvants include Freund's adjuvant (complete or incomplete), Adjuvant 65 (containing peanut oil, mannide monooleate and aluminum monostearate), the pluronic polyol L-121, Avridine and mineral gels such as aluminum hydroxide and aluminum phosphate (page 4-5).

Limitations such as the vaccine in a freeze-dried or spray-dried form is being viewed as process limitations.

Since the Office does not have the facilities for examining and comparing applicant's *Salmonella* vaccine with the *Salmonella* vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the *Salmonella* vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed *Salmonella* vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Marjarian et al is directed to bacteria carrying recombinant flagella carrying heterologous epitopes. Applicant also urges that Marjarian et al disclose vaccines that either consist of subunit flagellar proteins or live attenuated bacteria expressing flagella from recombinant plasmids. Applicant urges that the Office Action states that "Marjarian et al teach the use of a live attenuated expressing the recombinant flagellin genes of the invention used in the live vaccine formulations (page 9). Applicant urges that Marjarian et al approach requires that the flagellin gene be present. Applicant urges that Marjarian et al states that "the recombinant flagellin proteins are exported to the cell surface wherein they assemble into functional flagella containing the heterologous epitope". Applicant urges that Marjarian et al does not disclose flagellin minus bacteria as vaccines *per se* and the bacteria of Marjarian et al are employed as live vectors that enable expression of the recombinant flagellum within the infected host cell, through expression from an inserted plasmid carrying a flagellin gene-construct. Applicant urges that amended claim 14, with claims 17 and 18 dependent therefrom, define over this reference.

Applicant's arguments filed October 7, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that Applicant appears to argue limitations

that are not in the claims. The claims are drawn to a live attenuated vaccine for the protection of a subject against Salmonellosis comprising an immunologically effective amount of a mutated bacterium or mutagenic material thereof and a pharmaceutically acceptable carrier, said mutated bacterium being selected from the group consisting of the *Salmonella* species *typhi and paratyphi A and B*, that in its wildtype form carries flagella said mutated bacterium lacking at least one antigenic determinant of flagellin or flagella found in its wildtype form. There is no requirement in the claims that the flagellin gene in the mutated bacterium used in the claimed vaccines be absent. There is no requirement that the claimed vaccines should be minus bacteria. Marjarian et al discloses several different type of vaccine in the invention. For example, Marjarian et al disclose recombinant flagellin fusion proteins that can be formulated for use in subunit vaccines (page 45), disclose vaccines that disclose vaccines that are live attenuated bacteria that comprise heterologous epitopes (page 43). However, with the disclosure of subunit vaccines that comprise recombinant flagellin fusion proteins, Marjarian et al teach vaccines that are minus bacteria and do not require that the gene be present. Applicant asserts that "the bacteria of Marjarian et al are employed as live vectors that enable expression of the recombinant flagellum within the infected host cell, through expression from an inserted plasmid carrying a flagellin gene-construct", this is only one embodiment of the claimed invention and other types of vaccines have been described above. It should be remembered that the claims are drawn to a live attenuated vaccine; Marjarian et al disclose live attenuated *Salmonella* vaccines. It is the Examiner's position that there is nothing on the record to show that the live attenuated vaccine of

the prior art is not the same as the claimed mutated bacterium and vaccine. Therefore, the attenuated vaccines of Marjarian et al anticipate the claimed live attenuated vaccine.

New Grounds of Rejection

Claim Objections

8. Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutated bacterium does not reasonably provide enablement for antigenic material thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

The specification states that "mutation by transposon mutagenesis is a mutagenesis technique well known in the art" and that this a mutation that is accomplished at a localized site in the chromosomes" (page 8). The specification discloses chemical mutagenesis of a *Salmonella typhimurium* bacteria (pages 14-15). The specification does not disclose or define "antigenic material" of a mutated bacteria. What constitutes "antigenic material"? How much is antigenic material is used if a mutated bacterium is not present? The specification is not enabled for the use of "antigenic material". The skilled artisan cannot envision the detailed chemical structure of the encompassed antigenic material regardless of the complexity or simplicity of the method of isolation. Therefore, the specification fails to provide guidance regarding the use of antigenic material. One of skill in the art would require guidance, in order to make or use the antigenic material of an mutated bacteria in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation to is undue.

10. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutated bacterium does not reasonably provide enablement for antigenic material thereof. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

The specification states that "mutation by transposon mutagenesis is a mutagenesis technique well known in the art" and that this a mutation that is accomplished at a localized site in the chromosomes" (page 8). The specification discloses chemical mutagenesis of a *Salmonella typhimurium* bacteria (pages 14-15). The specification does not disclose or define "mutagenic material" of a mutated bacteria. What constitutes "mutagenic material"? How much is mutagenic material is used if a mutated bacterium is not present? The specification is not enabled for the use of "mutagenic material". The skilled artisan cannot envision the detailed chemical structure of the encompassed mutagenic material regardless of the complexity or simplicity of the method of isolation. Therefore, the specification fails to provide guidance regarding the use of mutagenic material. One of skill in the art would require guidance, in order to make or use the antigenic material of an mutated bacteria in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation to is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 7 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 recites "antigenic material", it is unclear as to what the Applicant is referring? Clarification is required.

12. Claim 14 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 recites "mutagenic material", it is unclear as to what the Applicant is referring? Clarification is required.

Status of Claims

13. No claims allowed.

Conclusion

13. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
December 22, 2002

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